

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
29 July 2004 (29.07.2004)

PCT

(10) International Publication Number
WO 2004/063190 A1

(51) International Patent Classification⁷: C07D 403/12,
405/12, 409/12, 413/12, 417/12, A61K 31/4155, 31/423,
31/427, 31/428, 31/437, 31/55, A61P 3/10, 29/00

IN 46060 (US). SCHKERYANTZ, Jeffrey, Michael
[US/US]; 9841 Deering Street, Fishers, IN 46038 (US).

(21) International Application Number:
PCT/US2003/041690

(74) Agents: DAVIS, Steven, G. et al.; Hamilton, Brook, Smith
& Reynolds, P.C., 530 Virginia Road, P.O. Box 9133, Con-
cord, MA 01742-9133 (US).

(22) International Filing Date:
31 December 2003 (31.12.2003)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR,
CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,
KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN,
MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU,
SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,
UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/438,541 6 January 2003 (06.01.2003) US

(84) Designated States (*regional*): ARIPO patent (BW, GH,
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,
SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): ELI
LILLY AND COMPANY [US/US]; Lilly Corporate
Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): CONNER, Scott,
Eugene [US/US]; 12461 Willow Bend, Elizabethtown,
IN 47232 (US). KNOBELSDORG, James, Allen
[US/US]; 10182 Parkshore Drive, Noblesville, IN 46060
(US). MANTLO, Nathan, Bryan [US/US]; 7325 East
County Road 800 North, Brownsburg, IN 46112 (US).
MAYHUGH, Daniel, Ray [US/US]; 9681 Troon Court,
Carmel, IN 47232 (US). WANG, Xiaodong [CN/US];
14066 Honey Tree Drive, Carmel, IN 46232 (US). ZHU,
Guoxin [CN/US]; 9972 Parkshore Drive, Noblesville,

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: FUSED HETEROCYCLIC DERIVATES AS PPAR MODULATORS

(57) Abstract: The present invention is directed to a method of treatment by modulating a peroxisome proliferator activated receptor by employing a compound of Structural Formula (I). The variables in I are defined herein. Also included are compounds, methods of making compounds, and pharmaceutical compositions. The compounds of the present invention are believed to be effective in treating and preventing Syndrome X, Type II diabetes, hyperglycemia, hyperlipidemia, obesity, coagulopathy, hypertension, atherosclerosis, and other disorders related to Syndrome X and cardiovascular diseases.

WO 2004/063190 A1

INTERNATIONAL SEARCH REPORT

PCT/US 03/41690

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D403/12 C07D405/12 C07D409/12 C07D413/12 C07D417/12
 A61K31/4155 A61K31/422 A61K31/423 A61K31/427 A61K31/428
 A61K31/437 A61K31/55 A61P3/10 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| P, X | WO 03/074051 A (FILZEN GARY FREDERICK ; GEYER ANDREW GEORGE (US); CHENG XUE-MIN (US) 12 September 2003 (2003-09-12) page 3, line 20 -page 7, line 14; claims 1,9-13,15; examples 3-12,14-18,18F,20,21,23-25 --- | 1-114 |
| X | WO 02/102780 A (ONO PHARMACEUTICAL CO ; TAJIMA HISAO (JP); TATSUMI TADASHI (JP); FU) 27 December 2002 (2002-12-27) abstract; claims; examples; table 1 & EP 1 405 848 A 7 April 2004 (2004-04-07) --- -/-- | 1-114 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

7 May 2004

Date of mailing of the international search report

21/05/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Hanisch, I

INTERNATIONAL SEARCH REPORT

PCT/US 03/41690

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | <p>RAMI H K ET AL: "Synthetic ligands for PPAR gamma - review of patent literature 1994-1999"</p> <p>EXPERT OPINION ON THERAPEUTIC PATENTS, ASHLEY PUBLICATIONS, GB, vol. 10, no. 5, 2000, pages 623-623, XP002257971</p> <p>ISSN: 1354-3776</p> <p>the whole document, in particular compound 5 in figure 3</p> | 1-114 |
| Y | <p>WO 02/060434 A (BOUERES JULIA K ;DESAI RANJIT C (US); KOYAMA HIROO (US); MERCK & C) 8 August 2002 (2002-08-08)</p> <p>page 24, line 6 -page 26, line 2; claims; examples 2,3,10,13,16-18,25,26,28</p> | 1-114 |
| Y | <p>WO 02/096904 A (SHIRAHASE HIROAKI ;KASAI MASAYASU (JP); KOBAYASHI HIDEO (JP); MATS) 5 December 2002 (2002-12-05)</p> <p>claims; examples 2-4,6-9,11</p> <p>& EP 1 398 313 A</p> <p>17 March 2004 (2004-03-17)</p> | 1-114 |
| Y | <p>WO 02/30895 A (BAYER AG)</p> <p>18 April 2002 (2002-04-18)</p> <p>claims 1,46-60; examples 209,212,220,240,356ETC</p> | 1-114 |

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 50-100 and 108-114 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 50-100,108-114

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Continuation of Box I.2

Claims Nos.: 1-11,19,28,29,38,47-62,70,79,80,89,98-100(all part)

Present claim 1 and all claims referring back to the current general formula relate to an extremely large number of possible compounds thereby encompassing known specific compounds. Besides the unlimited expressions "aryl", "heteroaryl", "aliphatic linker" etc. which among others may all be optionally substituted (see description) in particular the undefined connectivities give rise to a very large number of alternatives. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of claims 12-18,20-27,30-37 and 39-46 (which have in common that "E" represents "C(R3)(R4)COOH or COOH", "R2" is a bond and "R33" represents phenyl, optionally substituted by "R10 or R11", compositions containing the same and uses thereof. All of the examples are included thereby.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

PCT/US 03/41690

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 50-100, 108-114
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 1-11, 19, 28, 29, 38, 47-62, 70, 79, 80, 89, 98-100(all part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/US 03/41690

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|---|--|
| WO 03074051 | A | 12-09-2003 | WO 03074051 A1 US 2003207915 A1 | 12-09-2003 06-11-2003 |
| WO 02102780 | A | 27-12-2002 | EP 1405848 A1 WO 02102780 A1 | 07-04-2004 27-12-2002 |
| WO 02060434 | A | 08-08-2002 | CA 2427610 A1 EP 1347755 A2 WO 02060434 A2 US 2002103242 A1 | 08-08-2002 01-10-2003 08-08-2002 01-08-2002 |
| WO 02096904 | A | 05-12-2002 | CA 2448639 A1 EP 1398313 A1 WO 02096904 A1 | 05-12-2002 17-03-2004 05-12-2002 |
| WO 0230895 | A | 18-04-2002 | AU 1190102 A CA 2427499 A1 EP 1341761 A1 HU 0302477 A2 NO 20031619 A WO 0230895 A1 US 2003087902 A1 | 22-04-2002 18-04-2002 10-09-2003 29-12-2003 02-06-2003 18-04-2002 08-05-2003 |